

# Human Papillomavirus: Confronting the Epidemic— A Urologist's Perspective

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*The human papillomavirus (HPV) has long been associated with the development of penile lesions—condyloma acuminatum and verrucous carcinoma of the penis. More recently, HPV has been implicated as an etiology of more serious neoplasias in men—penile carcinoma and other anogenital squamous-cell carcinomas. HPV is now widely recognized as responsible for more than 95% of cervical cancers in women. HPV seems to have been receiving relatively scant attention to date—from physicians in general, and particularly from urologists—as a venereal disease of significant concern. Yet HPV is recognized to be the most frequently acquired sexually transmitted viral infection worldwide. It is estimated that approximately 6 million new cases of HPV are sexually transmitted annually in the United States. Fortunately, many, if not most, of these HPV infections are transient. However, each newly acquired infection has the potential to persist as an incurable, lifelong affliction, generating a significant increase in the long-term risk of cancer for patients and their sexual partners. Many of these HPV-related cancers will not become manifest until decades later.*

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**T**he terms “genital warts,” “condylomata acuminata,” “venereal warts,” and “genital HPV infection” have all been used to refer to lesions arising from the sexually transmitted human papillomavirus (HPV).<sup>1,2</sup> According to current understanding, HPV causes an infection of the squamous epithelium, and genital warts, precancerous lesions, and squamous cell neoplasms are the complications or diseases that follow.

Human papillomaviruses are DNA viruses. There are more than 100 types of HPV, at least 40 of which are sexually transmissible. These sexually transmitted HPV types are the cause of genital warts (condylomata acuminata). Of even greater concern is the fact that sexual transmission of the carcinogenic HPV types is responsible for the development of most, if not all, squamous cell malignancies that occur in the lower anogenital tract, in men and women alike.<sup>1-3</sup> (Common warts that affect the hands and other nongenital regions are caused by different HPV types, which are not sexually transmitted.<sup>3</sup>)

HPV types 6, 11, 42, 44, 53-55, and 66 have been associated with the development of benign neoplasms—condylomata acuminata and about one third of low-grade dysplasia. Viral types 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and others are associated with high-grade precancerous lesions and frank squamous cell malignancies of the lower anogenital tract and are considered high-risk viral types.<sup>4</sup> HPV-induced carcinogenesis includes the interactions of oncoproteins of high-risk types with host cells' anti-oncogenes pRb and p53, which stimulate the development of malignant change.<sup>4</sup> Carcinogenesis involves viral integration into the host-cell chromosome, inhibition of tumor suppression genes, loss of controlled cell growth,

mutation, and ultimately the development of dysplasia or cancer.<sup>4</sup>

Not only are at least 14 high-risk HPV types associated with squamous cell cancer, but for a given HPV type there are multiple variants with differing endemic geographic distributions and differing virulence. For instance, among Mexican women with cervical cancer, the Asian American variant of HPV16 is 21 times more prevalent than the European variant. It seems to cause cancer earlier and may be responsible for the development of adenocarcinomas, as well as squamous cell cancers.<sup>5</sup>

## A Sexually Transmitted Epidemic

It is estimated that approximately 6 million new HPV infections are acquired each year in the United States alone, and prevalence data suggest that as many as 24 million American adults—that is, 1 in 5—may be infected with HPV. In the population most at risk, those of reproductive age, as many as 75% may have been infected with genital HPV.<sup>6</sup> If so, HPV is the most commonly acquired sexually transmitted viral infection in the United States.<sup>6,7</sup> Recent estimates of the yearly cost for treating HPV and related diseases, including cervical cancer, exceed \$4.5 billion, more

than the cost of any other single sexually transmitted infection with the exception of HIV.<sup>8,9</sup>

Long before the AIDS crisis, warnings about epidemic HPV were being sounded. In 1954, military physicians first alerted the American medical community to the venereal transmission of genital warts. Soldiers returning from duty in the Far East had contracted penile warts there, and similar lesions were now developing on their wives' genitalia.<sup>10</sup>

Despite these warnings, the prevalence of symptomatic genital warts caused by HPV has skyrocketed during the last two decades.<sup>6</sup> Cervical cancer is now the first or second most common cause of cancer deaths among women throughout much of the developing world.<sup>8,11</sup>

## Condyloma Acuminatum

Human papillomavirus in genital condylomata can be highly contagious. It has been suggested that as many as two thirds of people who have sexual contact with a partner with genital warts may develop warts themselves, usually within 3 months of contact.<sup>7</sup> (Other studies, however, have found that a relatively small percentage of those who contract an HPV infection will develop manifest lesions.<sup>12</sup>)

### Condyloma Acuminatum in Men

These penile warts occur most commonly on the glans penis, penile shaft, and prepuce (Figures 1 and 2). Involvement of the meatus and urethra (occurring in approximately 5% of all cases<sup>4</sup>) constitutes a greater therapeutic challenge. Bladder involvement, though rare, can prove difficult to treat.<sup>4,13</sup>

Angiofibromata—so called pearly pink papules—are the multiple pale-pink nodules that appear circumferentially around the corona glandis after puberty in many men (Figure 3).

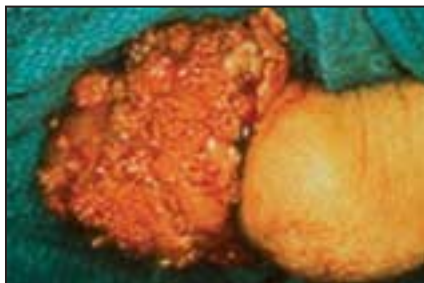


Figure 1. Florid example of extensive condylomata coating the entire distal penis. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.



Figure 2. (Left) Multiple, raised, warty lesions of the labia minora. (Right) Condyloma acuminatum with hyperkeratotic, papillary surface on the inner surface of the foreskin, extending onto the glans penis, in the male partner of the patient on the left. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.

These are not pathological and should not be confused with condylomata or aceto-white lesions.

#### *HPV in Semen*

The finding of HPV in semen has raised questions as to whether the presence of the virus can lead to decreased sperm motility and asthenozoospermia.<sup>14</sup> Caution must be exercised in providing donation of sperm from unscreened men,<sup>15,16</sup> lest the agent of cervical cancer be inadvertently transferred as well.

#### *Genital Condylomata in Women*

The presence of genital condylomata is not necessarily an indicator of an increased risk of cancer development, since they are caused by HPV types different from those which lead to cancer (Figure 2). Nevertheless, they are more than a cosmetic nuisance. The psychological impact of these unsightly, contagious lesions can have a profoundly negative effect, not only on a patient's sexual activity but also on her self-image and mental health. These warts may even present mechanical impediments to full enjoyment of coitus. Large condylomata have been known to block the birth canal, complicating delivery. Also, when vaginally transmitted during childbirth, HPV has led, on rare occasions, to the development of juvenile onset of recurrent respiratory papillomatosis, a highly debilitating disease that is potentially life-threatening.

#### *Malignant Transformation*

Although benign condylomata are considered the product of HPV types separate and distinct from those that lead to squamous cell cancer, instances of malignant transformation have been recorded.<sup>4</sup> It is not always clear whether the development of such cancers is due to true transformation or the concomitant presence of multiple HPV types leads to the develop-

ment of collocated benign and malignant lesions. A note of caution: If there is any doubt whether a condylomatous lesion is entirely benign, biopsy should be performed before the application of podophyllin, as this medication can induce histologic changes suggestive of carcinoma.<sup>4</sup>

#### **HPV: A Carcinogen in Men**

##### *Urogenital and Anal Malignancies*

Sexually transmitted HPV has been implicated in the development of dysplastic, precancerous, and cancerous lesions of the male genitalia, as well as of the anal region, including squamous cell cancer of the penis, verrucous carcinoma of the penis, and penile squamous intraepithelial neoplasias (ie, squamous cell carcinoma in situ, bowenoid papulosis, erythroplasia of Queyrat, or Bowen's disease of the genitalia).<sup>1,4,17,18</sup> Preliminary reports have also linked HPV transmission with the subsequent development of bladder and prostate cancers.<sup>4,18</sup> The concomitant presence of HIV may exacerbate an HPV infection and accelerate the malignant degeneration of indolent penile lesions.<sup>4</sup>

Squamous cell cancer of the penis, while considered rare in the continental United States, is not uncommon in Puerto Rico, throughout all of Latin America, and in many developing nations. Among men in many of

these regions, it constitutes one of the top 10 causes of cancer death. A combination of factors, including the absence of widespread circumcision, places men at a higher risk.

Bowenoid papulosis plays a unique role in the HPV spectrum of diseases<sup>4</sup> (Figure 4). Although this disease, unlike penile carcinoma in situ, has never been reported to progress to invasive squamous cell cancer, it is associated with HPV<sup>15</sup>, a cause of cervical cancer in women. Female partners of patients with this condition should be informed and followed up accordingly.<sup>19</sup>

A Scandinavian study has uncovered HPV DNA in 88% of cases of squamous carcinoma (but not adenocarcinoma) of the anal region, in both men and women.<sup>20</sup> These researchers concluded that "most anal cancers appear to be caused by sexually transmitted types of human papillomaviruses and, consequently, that anal cancer is a potentially preventable neoplasm."

#### *Men Having Sex with Men*

The large and growing number of patients with recurrent anal condylomata presents a clinical challenge, especially to surgeons who serve predominantly homosexual populations. Pain, embarrassment, and cost of care constitute a major burden for these



Figure 3. Multiple nodules on the corona glandis should not be confused with condylomata. These are angiofibromata, also called pearly pink papules. They develop after puberty and are present in about 20% of men. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.



Figure 4. Innocuous, small, subclinical papillary lesion on biopsy, contained penile intraepithelial neoplasia (bowenoid papulosis). The patient's female partner had high-grade squamous intraepithelial lesions of the cervix. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.

patients<sup>22</sup> (Figure 5).

More alarming is the escalating risk of anal cancer. HPV-transmitted squamous cell cancer is a problem of marked and widely unappreciated importance for homosexual men. The incidence of anal cancer among homosexual men exceeds that of cervical cancer in unscreened women.<sup>21</sup> And

Homosexual patients merit special attention from the urological community in 1) alerting these patients to the consequences of high-risk sexual activity, 2) screening for anal condylomata and other lesions during routine digital/rectal examination of the prostate, and 3) referring patients with condylomata to a gastroenterol-

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*HPV is the most frequently acquired sexually transmitted viral infection worldwide, with an estimated 6 million new cases annually within the United States.*

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this rate has been increasing over the past few years, in particular for HIV-positive men, among whom the rate is now approximately twice that of HIV-negative homosexual men.<sup>21</sup> In a recent survey conducted in France, 85% of sexually active male homosexual patients had anal cytology positive for HPV.<sup>22</sup> Overall, an Australian survey suggests, the presence of long-term HIV infection may increase the risk of anal cancer among homosexual men 34-fold.<sup>23</sup>



**Figure 5.** Intra-anal lesions in a man who engages in anoreceptive intercourse. In the majority of cases, these lesions do not extend higher than the external sphincter. Occasionally, they may be found as far as 5 centimeters proximally. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.

ogist for high-resolution anoscopy. Even if external condylomata are not themselves troublesome to the patient, they may constitute markers for more extensive internal condylomata and/or premalignant lesions within the anus and rectum.

### **Cervical Cancer in Women: Is Cervical Cancer a Sexually Transmitted Disease?**

In 1974, HPV was first recognized as a risk factor for cervical cancer. In that same year, Beral raised the question: "Is cancer of the cervix a sexually transmitted disease?"<sup>24</sup> HPV infection is now widely recognized as the principal etiologic agent in the development of cervical dysplasia and cervical cancer.<sup>8</sup> That is, the development of these cervical cancers is the result or complication of sexually transmitted HPV infection. The magnitude of this risk association is even greater than that between smoking and lung cancer.<sup>25</sup> (Smoking, it should be noted, is an independent risk factor that increases susceptibility both to HPV infection and to the development of cervical cancer.<sup>25</sup>)

The long-term use of oral contraceptives may increase susceptibility to HPV infection<sup>26</sup> and the subsequent development of invasive cervical cancer.<sup>27</sup>

Today, cervical cancer is a pandemic disease worldwide, and the rapidly escalating transmission of HPV<sup>6</sup> augurs even starker statistics for decades to come.

### **HPV: Other Squamous Cell Cancers**

Interestingly, HPV has been identified within a significant portion of all head and neck squamous cell carcinomas, raising the question: "Are some head and neck cancers a sexually transmitted disease?"<sup>28</sup>

### **Detection of Condylomata**

#### *Clinical Lesions*

The clinical detection even of overt lesions is not without its challenge. Lesions of the glans and distal shaft are most often clinically obvious. However, failure to retract the foreskin during routine examination can allow for important oversight. Smaller, flatter lesions along the mid and proximal shaft, as well as on the ventral surface of the distal penis, can be easily overlooked. Use of a magnifying glass may prove helpful. Peniscopy (also known as androscopy and peoscopy), using the colposcope to avoid missing subtle lesions has been advocated in the past but is no longer recommended.<sup>32</sup> Scrotal and crural lesions are especially easy to overlook. Asymptomatic anal and perineal lesions in young men may be categorically overlooked, during standard physical exams, now that routine digital rectal examinations are reserved to men over age 50 years.

#### *Subclinical Involvement*

At least half of the women who harbor HPV are asymptomatic carriers.<sup>25</sup> Some estimates suggest that less than 1 person in 100 infected with HPV has a clinically detectable lesion.

In many, if not most cases, the male partners of HPV-infected women harbor subclinical penile lesions that are undetectable by inspection alone.



Superficial application of 3% acetic acid to the penile shaft causes punctate areas of subclinical HPV infection to turn white—so-called aceto-white lesions.<sup>30</sup> However, false-positive and false-negative findings confound the clinical usefulness of this technique. Biopsies have shown that some of these aceto-white lesions are actually virus-free, whereas unaffected areas, when randomly biopsied, have proven positive. Extensive involvement of the entire penile shaft with such lesions presents a management challenge. And there is no proven clinical advantage to eradicating these aceto-white lesions, in forestalling either the clinical progression or the sexual transmission of the virus. For all of these reasons, the aceto-white test, while still recognized, has fallen into clinical desuetude.<sup>1</sup> Centers for Disease Control and Prevention (CDC) guidelines currently recommend against the pursuit and treatment of these subclinical lesions.<sup>17</sup> To depend on treating visible or subclinical condylomata as a cancer preventative leaves us attacking the wrong lesions at the wrong time in the wrong patients, while the spread of carcinogenic HPV progresses unabated.

### Cancer Detection

Screening for penile condylomata is unlikely to impede the transmission of oncogenic types of HPV. The strains of HPV associated with the development of benign penile lesions differ from those associated with the development of cervical cancer and other anogenital carcinomas. Because most men with carcinogenic HPV infections have no overt lesions, they can transmit the virus unknowingly to their sexual partners.

There is currently no practical screening test available to detect subclinical disease in men, and partners may already have been irreversibly infected with HPV by the time the

first clinical lesions appear either in the patient or his sexual contacts.<sup>8</sup> Although viral subtyping has been reserved thus far largely to research protocols, there is the hope that such testing might some day find at least limited clinical application in detecting potentially aggressive lesions earlier, to assist in treatment planning.<sup>3,8,31</sup> And yet, with about 100 HPV types of varying degrees of pathogenicity now

for 20 years or longer, before manifesting as a precancerous lesion of the cervix. In general, the latency period between persistent HPV infection and low-grade cervical dysplasia is 5 years, and between low-grade lesions and the development of invasive cancer is about 15 years. This relatively long time to progression is partly responsible for the successful reduction in the incidence and mortality

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### *The long-term use of oral contraceptives may increase susceptibility to HPV infection and the subsequent development of invasive cervical cancer.*

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harbored within the general population, definitive, wide-scale screening strategies seem far off, at best.

CDC guidelines currently advise:

A definitive diagnosis of HPV infection is based on detection of viral nucleic acid (DNA or RNA) or capsid proteins. Pap-test diagnosis of HPV does not always correlate with detection of HPV DNA in cervical cells. Cell changes attributed to HPV in the cervix are similar to those of squamous intraepithelial lesions and often regress spontaneously without treatment. . . . Screening for subclinical genital HPV infection using DNA or RNA is not recommended.<sup>17</sup>

Although these guidelines do not currently endorse screening examinations for asymptomatic sexual partners, it would nevertheless seem reasonable to suggest to male patients with genital warts that their female sexual partners undergo a standard pelvic and perianal gynecological examination, including cervical Pap smear, to detect the presence of subtle lesions. Both the patient and his partner may, in select cases, benefit from psychological counseling.<sup>32</sup>

### HPV Latency

It is estimated that HPV may be harbored in a latent (unexpressed) state

statistics for cervical cancers in industrialized nations, despite reliance on a relatively cumbersome and insensitive screening modality—the Pap smear.

Once infected with an oncogenic HPV type, patients with persistent HPV may remain at least intermittently capable of transmitting the disease to sexual partners throughout their lifetime.<sup>8,9</sup> This information is of clinical import in view of the increasing transmission of these viruses among adolescents and young adults.<sup>33</sup>

### HPV: The Sexually Transmitted Cancer Epidemic

Sexual transmission of HPV is widespread throughout the world today.<sup>34</sup> With respect to its benign sequelae, our colleagues in gynecology have characterized penile condylomata as “a gynecological epidemic disease.”<sup>35</sup> Worse still, HPV-related cancers are a pandemic venereal disease, and the penis is the primary vector of this viral carcinogen.

Squamous cell cancers of the male genitalia and anus, as well as cervical, vaginal, and anal cancers in women, and perhaps other squamous cell cancers, might arguably be counted as the late sequelae of a sexually transmitted infection—the HPV cancer epidemic.

And yet, as urologists—specialists in treatment of the male genitalia—we continue to show a remarkable lack of concern regarding this issue. As one indicator, among the more than 1877 abstracts presented to the annual convention of the American Urological Association for 2003, not a single item

evidence to indicate that blocking this secondary mode of contact has actually resulted in a reduced transmission of virus to a partner.

Speculation has been put forward that covering overt penile lesions with condoms during intercourse might reduce, although certainly not

HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners.<sup>38</sup>

#### *Surgery and Medications*

It is important to keep in mind that neither medical nor surgical treatment of discrete condylomatous lesions, no matter how complete their eradication, conveys proven protection against the subsequent transmission of benign or carcinogenic HPV. “Cured” (lesion-free) patients are still at risk of transmitting viral particles to their sexual partners. Only the patient's own immune system is capable of abolishing this virus.<sup>17</sup>

The makers of imiquimod cream, 5% (Aldara™, 3M Pharmaceuticals, St. Paul, MN) warn that the application of this product to the penis for the treatment of condylomata may adversely affect the integrity of condoms and diaphragms, potentially increasing the risk of transmission of this and other STDs.<sup>39</sup>

#### *Number of Sexual Partners*

The best protection against HPV is to avoid sexual contact with any person who might be carrying this virus. Research at the CDC confirms that the risk of contracting HPV is directly proportional to the number of one's sexual partners, and secondarily to the number of partners with whom one's partner has been in sexual contact.<sup>8</sup>

#### *Treatment of HPV Lesions*

The various treatment modalities for condylomata are well established and have been thoroughly described in standard texts.<sup>2</sup> CDC Sexually Transmitted Diseases Treatment Guidelines provide an excellent clinical summary.<sup>17</sup> Similarly, the diagnosis and treatment of penile cancers have been dealt with exhaustively in standard texts. A few observations,

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was related to HPV infection. Nor does a search of abstracts presented in 2002 uncover a single reference. In 2001, one abstract addressed this issue.<sup>18</sup>

#### **HPV Prevention**

##### *Condoms*

Whatever utility condoms may have in preventing transmission of other sexually transmitted diseases (STDs),<sup>7</sup> they provide no proven protection against the transmission of HPV.<sup>7,8</sup> This virus is directly transmitted by skin-to-skin genital contact and is not dependent upon exposure to semen or vaginal secretions (Figure 6).

HPV particles have been detected in the semen samples of known carriers.<sup>15,16</sup> Theoretically, condom use should decrease whatever small risk there may be of transmitting the virus in semen. However, there is no

exclude, viral transmission. And results from a meta-analysis suggest that, although incapable of preventing transmission of the virus, use of condoms may partially lessen the risk of subsequently developing clinically apparent warts or cervical cancer.<sup>36</sup>

Any diminution of risk condoms might provide is predicated on their correct and consistent usage. And yet, surveys consistently reveal that the meticulous and constant application of condoms is largely an unrealized ideal. Haphazard use is particularly prevalent among those at highest risk—adolescent and college-age men and women.<sup>33</sup>

##### *Vaccine*

Major attention has turned recently to the development of a vaccine against HPV infection. A report in the *New England Journal of Medicine*<sup>11,37</sup> has sparked nationwide interest in this potential, and preliminary studies suggest efficacy against HPV.<sup>15</sup> HPV vaccines, both as a preventive and a therapeutic intervention, are now receiving wide-scale international attention.

##### *Circumcision*

An international survey reported in the *New England Journal of Medicine* concludes that male circumcision is associated with a reduced risk of penile



Figure 6. Example of the proximal distribution of warts beyond the protective field of a condom. Photograph reprinted with permission of Alex Ferenczy, MD, BioVision, Inc., Quebec, Canada.

specifically relevant to HPV-related issues, warrant mention here.

#### *Condylomata: Subclinical and Minimal Lesions*

The value of vigorous detection and treatment of multiple minimal or even subclinical lesions is problematic. Early treatment of these minimal lesions may merely preempt their spontaneous regression. Spontaneous regression has been observed in two thirds of condylomata, over a 2-year period. Cell-mediated immune response plays an important role. On occasion, the application of dinitrochlorobenzene to a single wart has elicited regression of distant, untreated lesions.<sup>40</sup>

Although the majority of these lesions tend to resolve spontaneously, those that do persist may later prove refractory to standard therapy. Recurrence and persistence of recalcitrant condylomata challenge the urologist and dispirit the patient. It is empirically accepted that early treatment of small, but clinically evident lesions favors ease of eradication and also prevents the progressive development of multiple, larger, treatment-resistant lesions. Leaving lesions of the glans untreated may also lead to meatal and intraurethral migration of the virus. Thus, few urologists today would feel comfortable advocating "watchful waiting" over a 2-year period in the management of symptomatic penile condylomata.

#### *Condylomata: Topical Treatments*

Medical treatments of condylomata are subcategorized into 2 broad modalities. There are those time-honored topical treatments that are directly cytotoxic, such as podofilox, podophyllin, and 5-fluorouracil, as well as chemodestructive or keratolytic agents, such as salicylic acid, trichloroacetic acid, and bichloroacetic acid.<sup>2</sup> A second category

comprises immune-response modifiers. Imiquimod and interferon- $\alpha$  capitalize on this mode of action.

Imiquimod cream, 5%, the most advanced FDA-approved topical treatment, provides a model for what is best as well as what is most disappointing in the medical therapy of HPV, and highlights the need for further clinical research and development. Imiquimod has no direct antiviral activity<sup>39</sup>; rather, it induces cytokine activity within the host's own immune system. However, the clinical relevance of this induction remains uncertain. In a controlled study, only 39 of 109 treated patients (36%) were found to remain free of lesions 12 weeks after treatment.<sup>39</sup> Mild to moderate erythema was experienced by 61% of patients, and was characterized as severe in 4% of the cases. Moreover, this medication is not approved for use against cervical, vaginal, intraurethral, or rectal warts. Prospective patients are to be warned that "new warts may develop during therapy, as Aldara is not a cure."<sup>39</sup> Other topical agents present comparable limitations.

Initial reports indicate that the topical application of bacillus Calmette-Guérin (BCG) preparations can produce good results in the treatment of genital<sup>41</sup> and anal<sup>42</sup> condylomata.

Promising results have been achieved in stimulating a systemic resistance to the HPV-mediated lesions of recurrent respiratory papillomatosis through oral intake of a relatively innocuous phytochemical found in cabbage juice, indole-3-carbinol.<sup>43</sup> Investigations are now planned for testing the efficacy of indole-3-carbinol in the control of anogenital HPV lesions.

#### *Condylomata: Surgical Treatments*

Surgical approaches include electrocautery and cold-knife excision, as well as the use of carbon dioxide

laser ablation and cryotherapy. While more definitive in their immediate effect, these modalities are not necessarily more curative with respect to long-term outcomes, and they seem to have been subjected to even less in the way of controlled, prospective analyses.

#### *Intraurethral Lesions:*

##### *Detection and Treatment*

Detection and treatment of meatal and intraurethral lesions constitutes yet another area of controversy. Clinical questions center on whether and when to perform diagnostic urethroscopy. It has been estimated that intraurethral lesions may be present in as many as 33% of cases.<sup>44</sup> However, others place the estimate at less than 5%.<sup>4</sup> The incidence is highest when the presenting condylomata lie within close proximity to the meatus. The presence of urethral symptoms (such as dysuria or a urethral discharge) or an abnormal urinalysis should heighten the index of suspicion.<sup>1,44</sup>

When urethroscopy is indicated, timing of this intervention presents yet another dilemma. If the patient is undergoing regional or general anesthesia for the ablation of extensive external disease, convenience and patient comfort would seem to dictate that urethroscopy be performed under the same anesthesia. However, there is risk that the retrograde passage of the cystoscope might drag infected cells and viral particles into the urethra, thus initiating, in this virgin mucosa, the development of those very lesions that were to be detected and destroyed.<sup>44</sup> It is with this concern in mind that many urologists limit their urethroscopic inspection to the distal urethra, rather than risk contaminating the proximal urethra and bladder with infected debris. Others prefer to delay urethroscopy until after resolution of the external lesions is complete.

Antegrade and retrograde urethrography have been recommended as reliable modalities to screen for and follow the treatment-response of these lesions, while minimizing the risk of virus dissemination.<sup>45</sup>

### Treatment and Counseling—Summary

An external consultants' meeting convened by the CDC to promote research on HPV infection and its sequelae<sup>8</sup> recommended the following counseling guidelines:

- Persons with genital warts or cervical intraepithelial neoplasia should be informed about the high prevalence of HPV infection among adults who have been sexually active and the likely persistence of infection after treatment for an indefinite period of time.
- Those with monogamous partners should be counseled that their partners might already have been infected.
- No scientific data support the use of condoms specifically for genital HPV prevention; however, condoms should be recommended for the prevention of other STDs.
- Because duration of infectiousness is unknown and because genital HPV is so common among persons who have been sexually active, the value of disclosing a past diagnosis of HPV infection to future sexual partners is unclear, although candid discussions about past STDs should be attempted whenever possible.

### Urologists at Risk?

Direct hand-to-genital contact does not seem to play a significant role in the transmission of genital HPV. (There are sufficient data supporting the possibility of a minimal but real role for the nonsexual transmission of HPV that caution should be taken before assuming, when counseling a patient or parent, that the presence of

genital HPV categorically indicates sexual transmission—particularly when the social, psychological, and even penal ramifications of such an assumption might prove profound.<sup>46</sup> Nevertheless, the finding of genital or anal condylomata on a prepubertal child should raise an alert to the possibility of abuse.) The viruses that cause finger warts are site-specific and differ from those that cause genital condylomata and precancerous lesions.<sup>47</sup> Moreover, there are no evidence-based data to confirm that the use of latex gloves during examination of the male genitalia provides protection superior to that achieved through the simple practice of thorough hand-washing after each examination. (Some data do suggest that, at least theoretically, hand-genital transmission of noncarcinogenic HPV types may occur both in children<sup>49</sup> and in adults.<sup>47,49</sup>) Neither are there persuasive data to indicate that the examining physician is at risk of contracting HPV through hand-to-genital contact during physical examination or of transmitting the virus to subsequent patients.<sup>49</sup>

Nevertheless, the possibility of nonsexual transmission of HPV is still very much open.<sup>12</sup> For example, there is a possibility that reuse of nonsterilized vaginal specula could be a source of iatrogenic viral transmission.<sup>50</sup> HPV DNA has also been found on surgical gloves and biopsy forceps used in the care of patients with genital condylomata. Cryoprobe tips and biopsy forceps may still harbor HPV DNA, even after sterilization.<sup>40</sup> On the other hand, the detection of fragments of HPV DNA does not, of itself, prove the presence of transmissible HPV virus.

A more credible risk for the urologist is the inhalation of noxious viral particles during electrocautery or laser ablation of a penile condyloma. Experimental studies have confirmed

the presence of clinically active HPV particles within the plume of smoke from these instruments.<sup>51</sup> The case report of a laser surgeon who developed extensive laryngeal papillomatosis after providing laser ablation to patients with anogenital condylomata, lends clinical credence to this iatrogenic risk, not only for surgeons, but for other members of the operating room support staff, as well.<sup>52</sup> Suctioning the plume, assuring appropriate room ventilation, and wearing special mask protection should reduce this risk.

### The Urologist's Role

Urologists should be taking a leadership role in confronting the HPV epidemic. Not only in public information forums, but also—perhaps even more effectively—on a 1-to-1 basis, in our discussions with individual patients, valuable opportunities abound.<sup>33</sup> While educating our female patients is critically important, communication with our male patients warrants particular attention. Men seem to be significantly less informed about HPV. For example, in one survey of university students, 73% were unaware that HPV infection could be asymptomatic, and 39% believed that HPV did not affect men. Male respondents were, across the board, among the lowest scorers. And least well informed were those men who were most at risk, that is, those having sex with multiple partners and those who were disinclined to use condoms.<sup>53</sup>

Important strides have been made in recent years in encouraging urologists to include questions on impotence and erectile dysfunction as a routine part of patient interviews. However, incorporating similar questions related to at-risk sexual behavior seems to be receiving less enthusiastic acceptance within standard urologic practice.<sup>54</sup> And the time constraints imposed by contemporary



HMO-based practice militate against widespread improvement in this outlook anytime soon.

It would seem that we urologists should be joining with our colleagues in primary care, family practice, adolescent medicine, dermatology, preventive medicine, infectious disease, and gynecology, in raising the general level of awareness and concern, about this epidemic infection and its widespread, potentially lethal consequences. And yet, we need to do so in such a way that we avoid inciting undue alarm or panic, steer clear of being judgmental, and remain sensitive to the needs and concerns of our individual patients.

Ours should be a leadership role, as specialists in treating conditions of the male genitalia, not only in proactively addressing the issue among at-risk patients in our individual practices, but also in promoting public awareness of the HPV epidemic and its ramifications. Our leadership would also be greatly welcome in advocating clinical research and in actively educating our fellow health-care professionals about the management of this pervasive disease.

## Patient Information Resources

### Online

A word of caution: This roster of websites and telephone help-lines is intended to be a representative, not an

exhaustive, listing. The inclusion of a website on this roster does not indicate endorsement. All websites are not created equal. Each of these websites approaches the issue from a different perspective, offering different information and viewpoints, with different objectives in mind. Physicians would do well to preview any given website before recommending it to their patients. Patients, in turn, should check the information they obtain from these or any other websites against information that they have received from authorities they recognize as trustworthy.

#### NIAID Fact Sheet

<http://www.niaid.nih.gov/factsheets/stdhpv.htm>

#### National Cancer Institute

[http://cis.nci.nih.gov/fact/3\\_20.htm](http://cis.nci.nih.gov/fact/3_20.htm)

#### American Social Health Association

<http://www.ashstd.org/hpvcrc/index.html>

#### eMedicine: Gearhart PA, Randall TC, Buckley RM Jr. "Human Papilloma-virus"

<http://www.emedicine.com/med/topic1037.htm>

#### Medical Institute for Sexual Health

<http://www.medinstitute.org/products/index.htm>

Workshop Summary: Scientific Evidence for Sexually Transmitted Disease (STD) Prevention  
<http://www.niaid.nih.gov/dmid/stds/condomreport.pdf>

Indiana University Health Center  
<http://www.indiana.edu/~health/hpv.html>

University of Maryland  
<http://www.norharundel.com/ency/article/000886.htm>

ALDARA™ HPV Website  
[http://www.3m.com/us/health-care/pharma/aldara/con\\_std\\_hpv.jhtml](http://www.3m.com/us/health-care/pharma/aldara/con_std_hpv.jhtml)

### Telephone Help-Lines

American Social Health Association:  
(800) 230-6039

To subscribe to "HPV in Perspective" (15-page resource document) or "HPV Newsletter" online, call  
(919) 361-4848

CDC National STD and AIDS Hotline:  
(800) 227-8922 ■

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## Main Points

- Human papillomavirus (HPV) is the most frequently acquired sexually transmitted viral infection worldwide. Viral types 6, 11, 42, and 44 have been associated with the development of benign neoplasms, and viral types 16, 18, 31, 33, 35, 39, 45, and others are associated with high-grade precancerous lesions and frank squamous-cell malignancies of the lower anogenital tract.
- Whatever utility condoms may have in preventing transmission of other sexually transmitted diseases, they provide no proven protection against the transmission of HPV. This virus is directly transmitted by skin-to-skin, genital contact.
- Treatments for HPV lesions include topical treatments (eg, podofilox, salicylic acid, imiquimod) and surgery (electrocautery, cryotherapy, laser ablation). Information and counseling, particularly for male patients, is also an important part of treatment.
- Although the majority of condylomata resolve spontaneously, those that persist are often refractory to standard therapy. Removal of discrete condylomatous lesions, no matter how complete, does not ensure protection against the subsequent transmission of benign or carcinogenic HPV. Only the patient's own immune system is capable of abolishing this virus.

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